Section V: Conclusions

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Current Use of Medications In NATO Military Aircrew

The collection of data from NATO nations regarding use of medications for aircrew contains some interesting information and is a tool of great potential utility to NATO flight surgeons. In our survey of therapeutic medications use, we concentrated on medications used for long-term or sustained therapy for medical conditions. We did not survey nations on short-term therapeutic agents such as antibiotics.

As we stated in the introduction, there is a growing requirement to expand the range of medications available for use in aircrew. Allow me to repeat the list of factors driving these requirements:

- Rapid expansion of the number of new drugs available for clinical indications, offering enhanced disease management
- Diminished funding for research making it difficult for any single nation to completely evaluate aeromedical issues for one or more drugs
- Sustained round-the-clock operations and rapid deployment across multiple time zones
- Increased emphasis on mitigating the risk of chronic disease development through early intervention and improved disease management to reduce risk of disease complications
- Focus on population-based medicine leading to the understanding that consistently sound disease management, often involving newer pharmacologic agents, will maintain higher qualification rates in the aviation force
- Emphasis on force protection and emerging infectious disease threats increases demand for effective pharmacologic prophylaxis
- Absence of information on aeromedically significant effects of drugs from initial research required for licensure

Flight surgeons, particularly those serving in smaller nations, generally do not have access to the data to address aeromedical issues for newer medications. This makes decisions on aeromedical policy difficult. Access to experience and research from other nations can enable a sound aeromedical policy decision. The data set we have presented gives the flight surgeon the knowledge of which nations have information of potential use regarding a particular medication or class of medication. The potential advantages to the military service conducting air operations and to the individual aircrew member are considerable. As flight surgeons, we must strive to expand our options for use of medication in order to improve performance in the air operations we support and to give our aircrew the full benefit of the existing standard of care. Expansion of our options must, however, follow adequate evaluation of significant aeromedical issues. That is not to say that every potential aeromedical issue must be studied for every new medication considered—targeted evaluation based on risk assessment for a particular drug is a reasonable approach requiring aeromedical judgement.

Some NATO nations chose not to provide data for this database. Perhaps this reflects the sensitivity in some nations regarding use of medications by aircrew and the fear of generating the perception of chemically affected aircrew. Generally this sensitivity is more pronounced for operational medications. However, use of medications in military aircrew tends to be more restricted than that by civil aircrew and our Working Group has noted that occasional public interest in this topic abates with explanations of experience with the

Section I: Introduction

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Working Group 26 was originally chartered by the AGARD Aerospace Medicine Panel to study issues relating to use of medications in military aircrew. The group began its work in April, 1997 and was charged to continue its work by the newly created NATO Research and Technology Organization in 1998 following the dissolution of AGARD. Working Group 26 has completed its work under the auspices of the Human Factors and Medicine Panel.

Members

Table 1 shows the members of Working Group 26 as nominated by NATO member nations and appointed by the Aerospace Medicine Panel in 1997.

Table 1

Working Group 26 Members	
Col Mark Ediger - Chairman	United States
Air Cdre Anthony Nicholson	United Kingdom
Col Erich Rödig	Germany
Col Jeb Pickard	United States
Col Ronald Davidson	Canada
Dr. Gary Gray	Canada
Lt Col Daniele Danese	Italy
Lt Col Berry Lam	Netherlands
Lt Col Themis Eliopoulos	Greece
Med des Armees Philippe Doireau	France
Med en Chef Jean Francois Paris	France
Dr. Paul Kuklinski	Germany
Mrs. Barbara Stone	United Kingdom
Med Cdt Stephan van den Bemden	Belgium

The Issues

Flight surgeons and the military aircrew they support currently share heightened interest in expanding the list of medications known to be suitable for use in the military flying mission. Flight surgeons have traditionally taken a conservative approach to use of medications in military aircrew because of 1) the complexity, and lethality, of the weapons systems, 2) the physiologic demands of military aviation, and 3) incomplete information about side effects pertinent to the aviation environment. This conservatism has led to relatively few options for treating military aircrew for medical conditions. Available medications are generally limited to medications that have been in clinical use for a sufficient length of time for flight surgeons to be comfortable with their safety, or newer medications that research has shown to be safe in the aviation environment.

Over the past few years the limited aeromedical drug armamentarium has become too restrictive for flight surgeons and their aircrew. There has been growing frustration with the difficulties in gaining knowledge of aeromedically significant effects of medication. Working Group 26 was formed to seek out the means for cooperatively expanding our pharmacologic options in supporting military aircrew.

The following are the factors driving requirements in this area:

- Rapid expansion of the number of new drugs available for clinical indications, offering enhanced disease management
- Diminished funding for research making it difficult for any single nation to completely evaluate aeromedical issues for one or more drugs
- Sustained round-the-clock operations and rapid deployment across multiple time zones

- Increased emphasis on mitigating the risk of chronic disease development, through early intervention and reduction of risk factors
- Focus on population-based medicine leading to the understanding that consistently sound disease management, often involving newer pharmacologic agents, will maintain higher qualification rates in the aviation force
- Emphasis on force protection and emerging infectious disease threats, increasing demand for effective pharmacologic prophylaxis
- Absence of information on aeromedically significant effects of drugs from initial research required for licensure.

The Group's Working Process

Table 2 shows the goals and objectives established by the members of Working Group 26 in accordance with their taskings from the Aerospace Medicine Panel and the Human Factors and Medicine Panel.

The group was supported in its work by the member nations who provided the services of the members, whose expertise in aerospace medicine, pharmacology and clinical medicine enabled the group to attain its goals.

Information gathered by the working group was obtained in two ways: 1) via surveys of aerospace medicine leaders in NATO member nations, and 2) via literature research performed by members of the working group.

For the purposes of this report we define military aircrew as personnel with defined duties on board military aircraft. This definition is not limited to pilots, although the working group recognizes that aeromedical issues differ between crew positions.

Content of This Report

Information in this report concerns current use of medication in NATO aircrew, and the expansion of therapeutic and operational pharmacologic options. The first part of the report takes the form of literature reviews on the present state of the art in the pharmacologic treatment of disorders commonly encountered in the practice of military aviation medicine.

Information on current medication use is contained in the results of a survey sent to NATO member nations. We believe this data will be of considerable value to flight surgeons because it gives an overview of NATO nation policy and experience that is not available from any other source. Unfortunately, we were unable to obtain data from four NATO countries, but we believe the data remains very useful, and that this sort of data has great potential if we can keep it current.

Table 2

Working Group 26 Goals and Objectives	
Goal 1	**Create a database for medications in use by military aviators of NATO member nations**
	Obj 1 Define categories for medications in the data tables
	Obj 2 Establish what information will be contained in the database
	Obj 3 Gather data from member nations
	Obj 4 Establish means of access to the database for member nations
Goal 2	**Define the approach to determining the suitability of medications for use by military aviators and identify opportunities for collaboration between member nations in conducting aeromedical research on medications**
	Obj 1 Define the approach for therapeutic medications
	Obj 2 Define the approach for operational medications
	Obj 3 Describe the categories of aeromedical concern when evaluating drugs
	Obj 4 Describe the best means ("Gold Standard") for studying each category of aeromedical concern for medications
	Obj 5 Determine the capabilities of each member nation for conducting aeromedical research on medications, intramural and extramural
	Obj 6 Determine which drugs are candidates for immediate study
Goal 3	**Establish mechanisms for keeping the database current and for future determination of the suitability of drugs for use by military aviators**
	Obj 1 Identify a recommended means of updating and maintaining the database after the term of Working Group 26 has expired
	Obj 2 Develop a recommended mechanism for future collaboration in aeromedical research on medications
Goal 4	**Produce a report of the work products and recommendations of Working Group 26**

Information about expanding our therapeutic and operational options is contained in the final section, which discusses potential approaches to evaluating new medications. This is followed by recommended testing methods to evaluate specific aeromedical concerns in military aircrew, which we refer to as "gold standards." We believe that future sharing between NATO nations of aeromedical research on medication must include some commonly accepted measures ("gold standards") for evaluating specific aeromedical issues. The section concludes with a sample review of a candidate medication, in this case losartan potassium, with a possible approach to evaluation.

We consider this report to be an initial step towards cooperative evaluation of medications between NATO nations and sharing of experience with medications between NATO flight surgeons. The goal we should be able to achieve is an expanded knowledge of the aeromedical effects of medications and an expanded range of medication available for use in military aircrew.

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medications in question. We believe more open sharing of this information between NATO nations will be to the benefit of the air forces and their aircrew. We also believe the benefits will outweigh the risks of public misperception.

The data on use of agents for treatment of asthma in aircrew indicates there is considerable interest in keeping aircrew with mild asthma flying within the countries surveyed. Beta agonist therapy has long raised aeromedical concerns but they data does show considerable use of salbutamol in aircrew. Dr. Gray points out in his paper that expanded options in antiinflammatory therapy for asthma, including inhaled steroids, disosium cromoglycate, and leukotriene inhibitors, appear to hold some promise for control of mild asthma in aircrew.

Allergic rhinitis is a very common condition generally compatible with military aircrew duties while under treatment. The data collected shows widespread use of inhaled steroids in military aircrew. Most interest has focused on the use of H1 antihistamines for this condition in aircrew because of their superior therapeutic response. The data shows that several nations have forbidden the use of terfenadine and astemizole in aircrew, while several nations are using loratadine. The paper by Dr. Davidson et al points out that loratadine and fexofenadine appear to hold the most promise for treating military aircrew for allergic rhinitis, although full data is not yet available on cognitive effects.

Among digestive disorders, reflux esophagitis and dyspepsia are the two conditions most often requiring sustained therapy in aircrew. Our survey did not include antibiotic therapy for peptic ulcer disease since that therapy is used for a finite, relatively short course of treatment. The data shows that side effect concerns have led several nations to specifically forbid the use of metoclopramide and cisapride. Antacids, omeprazole, and ranitidine are the most widely used agents for dyspeptic and reflux symptoms in military aircrew among the nations surveyed. Considerable aeromedical experience appears to be accumulating for these agents. The common use of mesalamine and sufasalazine in aircrew most likely reflects good experience with keeping aircrew with mild or limited inflammatory bowel disease in flying duties.

The treatment of hypertensive aircrew primarily is carried out to prevent long-term rather than near-term health complications. For many years, treatment options available to flight surgeons were limited to thiazides, leading to marginal or inadequate control in many aircrew, whose only other option was grounding. The data now reflects considerable use of angiotensin converting enzyme inhibitors, particularly enalapril and lisinopril, and considerable use of the beta blocker, atenolol, in aircrew. Dr. Pickard's paper shows us the continuing need for more options in treating hypertensive aircrew. The 20% incidence of cough with ACE inhibitors and the side effects from beta blockers (particularly in high performance aircraft) make these agents unsatisfactory for too many military aircrew. Dr. Pickard points out that angiotensin II converting enzyme inhibitors, such as losartan, appear to hold promise for use in aircrew and would be a significant addition to treatment options available to military flight surgeons. Dr. Pickard's paper proposing a study protocol for further evaluating the aeromedical suitability of losartan led our group to designate losartan as a drug in need of immediate study.

Evidence is mounting favoring treatment of moderate LDL cholesterol elevations as primary prevention of coronary artery disease. The advent of the HMG CoA reductase inhibitors (statins) gave us lipid-lowering drugs with side effect profiles compatible with use in military aircrew. So great was the interest around 1990 in this therapy for primary prevention, we saw nations proceeding with use of lovastatin prior to availability of good studies on cognitive performance effects. Dr. Eliopoulos reviewed aeromedical issues in lipid lowering therapy in his paper, including the fact that we now know lovastatin penetrates the blood-brain barrier and has measurable effects on sleep and cognitive performance (as do other lipophilic statins). Despite this, there have been no reports of aircraft incidents or accidents attributable to aircrew on lovastatin therapy. The data collected in our survey now shows widespread use of pravastatin and simvastatin in military aircrew. Dr. Eliopoulos makes the point that pravastatin is the only hydrophilic statin and thus has no significant penetration of the blood-brain barrier. This, along with the measured effects on sleep and performance in the lipophilic statins, makes pravastatin the optimum choice for treatment of LDL cholesterol elevations in military aircrew.

Our survey did not include medications for psychiatric disorders, but in discussions since conducting our survey we recognized that the use of selective serotonin/norepinephrine reuptake inhibitors has become quite common in treatment of depression and anxiety disorders. Informal surveys indicate that military air forces are keeping aircrew grounded while on these medications, but the significant incidence of these conditions and the need to encourage aircrew to seek treatment warrants consideration of the suitability of these medications for use while performing flying duties. Some significant aeromedical issues, such as sleep disturbance, need to be carefully evaluated before their use is considered in military air operations.

The continuing emergence of drug resistance in *Plamodium falciparum* around the world raises signficant concern about chemoprophylaxis in military aircrew. Our data shows that chloroquine and doxycycline are the most commonly used agents. Due to chloroquine resistance in many locations, doxycycline has become the primary means of protecting aircrew from malaria. Recent emergence of doxycycline resistance is has generated interest in the possibilities of using mefloquine in aircrew. Dr. Paris' paper includes a review of the available information on mefloquine side effects, which is a fascinating topic. Reports of serious psychiatric side effects and anecdotal reports of CNS side effects have led most nations to prohibit use of mefloquine in military aircrew. However, some nations do use mefloquine and their experience with it has been favorable. In fact, Dr. Paris summarizes several studies showing superior compliance and lower side effect rates among military members taking mefloquine in comparison to those taking chloroquine or doxycycline. Also, Dr. Paris point out that more recent studies suggest that the incidence of CNS side effects with mefloquine have been much lower than reported in earlier studies. Even so, CNS side effects, particularly those involving psychosis, generate much caution about their use in military aircrew. The evolving need for an alternative to doxycycline and the controversy about the side effects of mefloquine led our group to designate mefloquine as a drug in need of immediate aeromedical study. Ideally, a breakthrough in preventive measures for malaria will eliminate the need for chemoprophylaxis—but until that occurs, more options for prophylaxis are needed.

The advent of night air operations and rapid long-range deployment have increased interest in pharmacologic support of sustained operations. In particular, the use of stimulants to improve performance during prolonged periods without sleep is of greatest interest. Caffeine and dextroamphetamine are the stimulants with which certain nations have the most experience, but our data shows interest in finding improved alternatives. Although the operational experience with dextroamphetamine has been good, the potential for abuse and potential for side effects generate concern among flight surgeons. The dehydrating effects of caffeine limit its usefulness in physically demanding situations. As discussed in Dr. Nicholson's paper, this interest is focused now on modafanil, sustained release caffeine, and pemoline. Modafanil, a noradrenergic agent, and pemoline, a dopaminergic agent, hold promise as stimulants with less potential for side effects in comparison to dextroamphetamine. Several nations report studies underway on modafanil, but Dr. Nicholson's review indicates that pemoline is also a stimulant worthy of immediate study.

The Approach to Evaluating New Medications

Dr. Nicholson and Dr. Pickard have described and discussed the approach to evaluating medications to determine suitability for use by military aircrew. Evaluation of therapeutic and operational drugs shares several common characterisitics, but significant differences also exist.

Dr. Pickard explained the importance of first selecting a drug or class of drugs that will achieve the desired therapeutic end-point while posing minimal risk of aeromedically signficant side effects. The risk of such side effects has traditionally posed the most vexing question for flight surgeons. Dr. Pickard makes the point that military aviation is an occupation demanding high levels of performance and posing high levels of risk, making certain subtle side effects threatening to safety and the mission. These side effects, such as cognitive impairment or mild orhtostatic blood pressure changes, can be so subtle that prelicensure studies for the commercial market seldom address them, leaving the flight surgeon wanting for very important information. A medication with a long clinical track record adds some degree of comfort regarding side effects, but doesn't adequately address concerns about subtle, aeromedically significant side effects.

Operational medications often are directed at helping aircrew sustain performance over prolonged sleepless periods or deal with the effects of circadian desynchronization. Use of these medications to enhance performance in healthy individuals often falls beyond therapeutic experience with the drug, leaving a greater gulf between information needed by the flight surgeon and information available. Dr. Nicholson discusses the importance of verifying that the drug will reliably enhance performance in an operational setting. He stresses the importance of measuring relevant aspects of performance in ways that translate well into performance in the aircraft. He cautions against the common tendency to assume that simulator studies translate into operationally valid conclusions.

The approaches to evaluating new medications for aeromedical use described by Dr. Pickard and Dr. Nicholson are critically important to the aircrew and missions we support as flight surgeons. Recent history holds several examples of medications pressed into use in aircrew in a rush of enthusiasm (often propelled by commercial marketing) only to be withdrawn when aeromedically significant side effects come to light. Conversely, we do a disservice to all concerned if we rigidly adhere to protracted courses of evaluation over periods of years before considering a new medication. The right balance must embrace scientific evaluation of the most likely areas of aeromedical risk for a particular drug while accepting some degree of aeromedical risk for less likely side effects. Such a balance is most likely to enable us to be sufficiently responsive to those we support while fulfilling our duties to effectively use medication at minimal risk.

Ethical Issues

We must take care not to focus only on scientific facts when making decisions about operational or therapeutic use of medications in military aircrew. In this author's paper on ethics, the three spheres of influence when making such decisions were: 1) the law, 2) scientific facts, and 3) ethics. Experiences in the last decade, such as the controversy about Gulf War Illness, have reinforced the importance of considering all three spheres in our decisions.

Each nation has its laws governing the use of medications and sometimes these laws affect our ability to use medications for operational purposes. In some nations, documented informed consent is necessary. As part of a physician's duty to inform and obtain consent, the flight surgeon must ensure such consent is truly voluntary and ensure the aircrew are fully informed about the medication's effects and risks.

The flight surgeon has the duty to ensure disease in military aircrew is treated in accordance with the existing standard of care so that the long-term health of the aviator is not compromised. Likewise, the flight surgeon must ensure that mission enthusiasm does not lead to circumvention of the basic duty to communicate and manage risk.

Full consideration of the ethical sphere of influence is essential for future decisions about expansion of medications in use by military aircrew, both therapeutic and operational.

Gold Standards

The working group's paper on "gold standards" provides our conclusions about the most widely accepted means of assessing particular types of aeromedical risk. We believe use of such gold standards when studying medication for aeromedical risk is essential to producing valid answers useful to all nations with whom that data may be shared.

Of course, any list of scientifically accepted standards of evaluation will change over time with the advent of new knowledge and new technology. Agreement on such standards will be a cornerstone to any future cooperative research. Our paper on gold standards is an effort to publish standards as a starting point and source of information for cooperative research on aeromedical suitability of medications.

Need for Immediate Study of Certain Medications

After extensive study of operational requirements, aeromedical issues, and pharmacologic information, the working group has concluded there is a compelling need for immediate study of stimulants, antimalarials, angiotensin blocking agents, ultra short-acting hypnotics, and selective serotonin/norepinephrine reuptake inhibitors. Study of these types of drugs would be of

immediate benefit to NATO air forces and their aircrew.

Sustained operations in our air forces demand improved pharmacologic support to enhance safety and effectiveness for the aircrew. As pointed out in this publication's papers by Dr. Nicholson and the reprinted paper by Dr. LaGarde, pemoline and modafanil appear promising as safer stimulants for effective enhancement of performance during prolonged operations. Dr. Nicholson also proposes the ultra short-acting hypnotic agents as potential aids to brief napping to enhance performance.

The evolution of resistant strains of *Plamodium falciparum* and questions about the true incidence of side effects render mefloquine a prime candidate for immediate study.

The need to retain aircrew with mild to moderate hypertension, of which there are many, while protecting their future health leads us to urge the immediate study of angiotensin blocking agents, such as losartan.

Depression, anxiety disorders, and their treatment with selective serotonin/norepinephrine reuptake inhibitors are relatively common and, in many cases, the individual aircrew member does return to flying duties. The prolonged nature of the treatment, the need to retain trained aircrew, and the need to encourage identification of those in need of treatment all point to the importance of studying these medications immediately.

Dr. Pickard's description of a study protocol for evaluating the aeromedical suitability of losartan is an excellent example of the kind of road map that should guide such studies.

Working Group 26 Proposals

We believe the tables provide details on aeromedical usage of medication that has only previously been available anecdotally. Access to such information will be of significant value to NATO flight surgeons and the air forces they support. Not only will this information enable more expeditious policy changes about medication use in military aircrew, but it will help avoid duplication of research and encourage cooperative research between nations. Annual updates of this data and its continuing availability to NATO flight surgeons is essential to its utility. Our working group believes this data would best serve the mission as part of an official NATO publication subject to regular updates and expansion to include data from all NATO air forces.

We believe we have clearly established that our air forces and their aircrew require expansion of the range of medications known to be suitable for use in military aircrew. We believe we have also established that certain questions about aeromedical risk must be addressed before such expansion can occur. The primary constraints to expansion of available medications for military aircrew are funding and availability of particular types of aeromedical research capability. Our working group believes cooperative studies in which various nations contribute in their areas of research capability on a given medication would be most resource efficient and expedite the process considerably.

In particular, we believe consortia of NATO nations cooperating on the study of aeromedical questions pertaining to the medications we have identified for immediate study would be of great benefit. We strongly encourage prototype studies of some of these medications to demonstrate the feasibility and benefits of this cooperative international approach.